BIOLOGICALLY ACTIVE IMPLANTS

Cross-Reference to Related Applications

This application is a continuation of the U.S. National Stage designation of co-pending International Patent Application PCT/EP99/06708, filed September 10, 1999, which claims priority to German Application No. 198 43 251.8, filed September 11, 1998. The entire content of both of these applications is expressly incorporated herein by reference thereto.

Field Of The Invention

The present invention relates to an implant designed to compensate for pathological changes or conditions in the spinal column and/or locomotor system. The invention also covers a method for producing such an implant.

Background Of The Invention

Implants for treatment of pathological conditions of the spine and/or locomotor system are known in the prior art. They are intended, for example, to mechanically stabilize a fracture, thus promoting the healing process or, in the case of endoprosthetic implants, to be permanently bonded to the bone.

PCT Publication No. WO 98/19699 describes the systemic administration of medications or hormones serving to promote osteosynthesis and thus to accelerate the healing process of the fracture. Examples of suitable means include growth factors such as IGF-I. Such systemic applications, however, can lead to undesirable side effects.

PCT Publication No. WO 93/20859 describes the fabrication of a thin foil or film consisting of a polylactic-acid/polyglycol-acid copolymer containing growth factors. The intent is to wrap a foil of that type, for instance, around fracture-fixation devices prior to their implantation. This is supposed to release the growth factors in localized fashion in the area of the fracture. In practice, however, this method is unsuitable since, for instance, a nail wrapped with a foil of that type cannot be inserted in the medulla in a way that the foil, which only loosely envelops the nail, actually reaches the point of its intended healing action.

In light of the foregoing, a need exists for an implant that promotes the healing process in pathological changes of the spinal column and locomotor system, especially by

furthering osteosynthesis, and thus accelerating the healing of fractures or the integration of an implant.

Summary Of The Invention

5   The present invention relates to an implant for treating pathological changes or conditions in the spinal column and/or locomotor system. The implant, in various embodiments, has a varnish-like biodegradable polymer coating of a thickness of 100 μm or less, a thickness of 50 μm or less, preferably 30 μm or less, and more desirably, 20 μm or less. In other embodiments, the varnish-like coating has a thickness of 10 to 30 μm, and

10   preferably 10 to 20 μm. The implant can be a fracture-fixation device or an endoprosthetic device. Examples of such devices include plates, screws, nails, pins, wires, threads, or cages used for the spinal column and locomotor system.

The polymer used for the coating may have a glass transition temperature of 37°C (98.6°F) or higher and a mean molecular weight of 100 kDa or less. Examples of suitable

15   polymers include poly-α hydroxy acids, polyglycols, polytyrosine carbonates, starch, gelatins, and cellulose, as well as blends and interpolymers thereof. Examples of suitable poly-α hydroxy acids include polylactides, polyglycol acids, and interpolymers thereof.

The varnish-like coating according to the present invention can also include pharmaceutically active additives, such as osteoinductive substances. Examples of such

20   substances include one or more growth factors. Specifically, the growth factors can be selected from the group consisting of IGF, TGF, FGF, EGF, BMP, and PDGF. In an exemplary embodiment, the coating contains IGF-I, TGF-β, or combinations thereof. In one embodiment, the growth-factor percentage of the total weight of the coating is 0.1 to 10% by weight, preferably 0.5 to 8% by weight and, more desirably, 1 to 5% by weight.

25   The present invention also relates to a method of producing an implant having a varnish-like biodegradable polymer coating of a thickness of 100 μm or less. Furthermore, the invention relates to an implant produced by such a method. The method for producing an implant includes the following steps: preparing a dispersion of the biodegradable polymer in an organic solvent; applying the dispersion on the surface to be coated; and

30   allowing the solvent to evaporate. The application and evaporation processes may occur, for example, at a temperature of between 0 and 30°C (32 - 86°F), and preferably at about 22°C (72°F). Additionally, the evaporation of the solvent may occur, for example, in a gaseous atmosphere substantially saturated with solvent vapor. In an exemplary embodiment, the application of the dispersion and the evaporation of the solvent are

35   repeated two or more times.

The dispersion may be a colloidal solution of the polymer in the solvent. Such a colloidal solution may be produced by allowing a mixture of polymer and solvent to stand for periods of time ranging from 1 minute to 24 hours, preferably 2 to 24 hours, 3 to 12 hours, or 4 to 8 hours, and most preferably for about 6 hours. The colloidal solution may be

5   filtered prior to its application. The filtering may occur through a micropore filter with a pore size of 0.45 μm or smaller.

Suitable solvents include ethyl acetate or chloroform with the dispersion containing, for example, 20 to 300 mg of polymer per ml of solvent.

10 Brief Description Of The Drawings

Preferred features of the present invention are disclosed in the accompanying drawings, wherein similar reference characters denote similar elements throughout the several views, and wherein:

Fig. 1 shows the degradation of a polylactide coating on an implant according to the

15 present invention as a function of time both *in vivo* and *in vitro*;

Fig. 2 shows the release of growth factors contained in the polylactide coating as a function of time;

Fig. 3 shows a radiographic comparison of the effect of implants having a coating according to the present invention versus untreated (uncoated) implants on fracture healing

20 in rats;

Fig. 4 shows a biomechanical comparison of the implants of Fig. 3;

Fig. 5 shows a histomorphometric comparison of the implants of Fig. 3;

Fig. 6 shows illustrations of histomorphometric examinations;

Fig. 7 shows a radiographic comparison between coated and uncoated implants in

25 Yucatan pigs;

Fig. 8 is a biomechanical comparison of the implants of Fig. 7; and

Fig. 9 shows the maximum torsional load and torsional stiffness in another examination of tibia fractures in rats.

30 Detailed Description Of Preferred Embodiments

The present invention relates to an implant having a varnish-like coating of a biodegradable or resorbable polymer that may be up to 100 μm thick. As used herein, the term *implant* refers to a device, which in the process of a surgical procedure is at least partially introduced inside the body. In an exemplary embodiment, the present invention is

35 directed to implants of the type that serve to support a pathologically changed spinal column

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and/or locomotor system, especially by providing a mechanical reinforcement. The pathological changes may be in the form of fractures, pathological changes of joints and bones, distended or torn ligaments or tendons and the like. Application of the implants may involve direct contact with, attachment to or insertion in a bone of other part or element of

5   the spinal column or locomotor system (such as ligaments or tendons).

The term *implant* is to be understood in the broadest sense of the word since it also includes, for instance, implants which are used for elongative or reductive ostectomies, craniotomies, for ligament healing and restoration, for tumor and sports-injury-related surgery, in dentistry as well as in the case of oral, maxillary and facial dislocations.

10   The term *fracture fixation device* refers to any device that serves to fix, correct and/or mechanically stabilize a fractured bone. Examples thereof include plates, screws, nails, pins, wires, sutures, or cages for the spinal column and locomotor system. Usually, fracture fixation devices are removed after the fracture has healed, but in certain circumstances, they may be permanently left in or on the bone or they can be reabsorbed by

15   the organism. Endoprosthetic implants are designed to permanently remain in the body and usually function as substitutes for a natural body part such as a joint, a bone section or a tooth.

The implants according to one embodiment of the invention are made of a base material that is chemically and/or physically different from that of the varnish-like coating.

20   In many cases, the base material may not be biodegradable. This implies that under physiological conditions, where the implant is used and for the length of time during which it is typically retained in the body, the base material will not decay, corrode or in any other way change its physiochemical state, or if it does, then only with negligible deterioration of its desired effect. An implant according to one aspect of the invention will in many cases

25   consist of a metal or an alloy such as stainless steel or titanium. Alternatively, the implant may consist of a base material which is itself biodegradable or bioresorbable.

In accordance with the present invention, the implants are provided with a varnish-like coating. The term *varnish-like* means that the coating bonds with the surface of the base material with enough adhesive strength such that, when the implant is implanted,

30   mechanical friction will not abrade or otherwise damage the coating, or at least, not to such an extent as to compromise its physical effect, as described in more detail further below. For example, it is advantageous to properly drive a nail, provided with the varnish-like coating, into the bone without any significant abrasion of the varnish-like coating.

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The coating may be up to 100 μm thick. In other words, it is preferable that the average thickness of the coating is 100 μm or less. For example, spots with a thickness of more than 100 μm, occasioned by fluctuations in the coating process, would be allowed.

The coating consists of a biodegradable polymer. This means that, due to its

5 exposure to the physiological conditions prevailing in the area of the implant, it will progressively degrade, over a period of preferably several weeks, months, or years, through molecular breakdown. These molecular separation products and any other metabolites preferably display no or, at worst, only negligible toxicity and the body should be able to metabolize or excrete all or most of them. Polymers, which contain no toxic metabolites

10 and can be completely biodegraded and eliminated, are also sometimes referred to as *bioresorbable*. The polymers used in applying this invention are preferably of the bioresorbable type.

It is surprising that, even without the addition of other pharmaceutically active agents such as growth factors, the varnish-like coating promotes osteosynthesis (and thus

15 contributory fracture-healing, infection-fighting, and complication-avoiding effect).

The thickness of the varnish-like coating is preferably 50 μm, more preferably about 30 μm, and most preferably about 20 μm or less. In many cases, the preferred thickness is between 10 and 30 μm and most desirably between 10 and 20 μm.

The polymer employed preferably has a glass transition temperature of 37°C

20 (98.6°F) or higher so as to retain its desired strength in the body. Polymers with a mean molecular weight of 100 kDa or less are preferred.

The polymer is preferably selected from the group comprising poly-α-hydroxy acids, polyglycols, polytyrosine carbonates, starch, gelatins, cellulose as well as blends and interpolymers containing these components. Particularly preferred among the poly-α-

25 hydroxy acids are the polylactides, polyglycol acids, and their interpolymers. One example of a suitable polylactide is marketed by Boehringer-Ingelheim under the trade name R 203. It is a racemic poly-D,L-lactide. This racemic compound forms an amorphous, varnish-like layer on the surface of the implant. The formation of crystalline polymer structures in the coating should preferably be avoided, which is why an enantiomerically pure lactide is

30 preferably avoided. Suitable polytyrosene carbonates include for instance p(DTE-co-5% PEG 1000 carbonates) and p(DTE-co-26% PEG 20000 carbonates). These are copolymers containing the specified amounts of polyethylene glycols.

The coating may contain additional pharmaceutically active agents, such as osteoinductive or biocidal or anti-infection substances. Suitable osteoinductive substances

35 include, for example, growth factors whose proportion of the total weight of the coating is

preferably 0.1 to 10% by weight or, more preferably, 0.5 to 8% by weight and, most desirably, 1 to 5% by weight. This weight percentage relates to the net amount of the active agent, without counting any pharmaceutical carrier substances.

5   The growth factors may be selected from the group of IGF (insulin-like growth factors), TGF (transforming growth factors), FGB (fibroblast growth factors), EGF (epidermal growth factors), BMP (bone morphogenic proteins) and PDGF (platelet-derived growth factors). These growth factors are well known and are commercially available. The varnish-like coating preferably contains the IGF-I or TGF-β growth factors, with particular preference given to a combination of these two growth factors.

10   This invention also relates to a method for producing an implant of the type described above, which may include the steps of:

- Preparing a dispersion of the biodegradable polymer in an organic solvent;
- Applying the dispersion on the surface to be coated; and
- Allowing the solvent to evaporate.

15   The term dispersion refers to any given distribution of the polymer in an organic solvent. This may be a chemical solution, a purely physical dispersion or any intermediate step, especially including for instance, colloidal solutions. The application of the dispersion and the evaporation of the solvent preferably take place at a temperature of between 0 and 30°C (32 - 86°F), and more desirably at a room temperature of about 22°C (72°F). This so-

20   called cold coating also allows for temperature-sensitive components such as certain growth factors to be applied on the implant together with the polymer. Applying the dispersion is performed preferably by immersing the implant in the dispersion. Other ways of applying the coating, for example by brushing, spraying, etc. are also possible. Of course, in addition to the polymer, the dispersion may also contain the aforementioned pharmaceutically active

25   agents such as osteoinductive or biocidal substances.

Most preferably, the solvent is allowed to evaporate in a gas atmosphere, essentially saturated with solvent vapor. To that end, it is desirable to manipulate the implant that has been immersed in the dispersion, in a closed space whose atmosphere is highly solvent-saturated. Preferably, this will result in a very slow evaporation of the solvent, and

30   consequently, in a uniform, well-adhering varnish-like coating. The preferred evaporation time is between 1 minute and 1 hour, or more preferably 5 to 30 minutes, and most desirably about 10 minutes. It is also preferred to apply the coating by incrementally building it up in several thin layers, for example by repeating the dispersion and the solvent-evaporation processes two or more times.

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Preferably, a dispersion which is constituted by a colloidal solution of the polymer in the solvent may be used. This colloidal solution preferably contains colloidal polymer particles between 1 and 1000 nm and preferably less than 400 - 500 nm in size. For example, this type of colloidal solution can be produced by mixing the polymer and the solvent, then letting it stand for a period of 1 minute to 24 hours, preferably 2 to 24 hours, more preferably 3 to 12 hours, still more preferably 8 hours, and most desirably about 6 hours. During the most preferred period of about 6 hours, polymer colloid particles will form in the desired size range of less than about 500 nm. To separate any remaining larger polymer particles, the colloidal solution can be filtered prior to its application on the implant, preferably by using a micropore filter whose pore size corresponds to the desired maximum size of the colloid particles. Micropore filters are commercially available with pore sizes for example of 0.45 or 0.2 μm.

The solvents used are preferably popular organic, nonpolar or weakly polar solvents. Particular preference may be given to ethyl acetate or chloroform. Prior to its application on the implant, the dispersion preferably contains an amount of, preferably 20 to 300 mg, and more desirably 50 to 150 mg, polymer (perhaps including other constituents such as osteoinductive or biocidal substances) per ml of solvent.

These and other aspects of the present invention may be more fully understood with reference to the following non-limiting examples, which are merely illustrative of the preferred embodiments of the present invention, and are not to be construed as limiting the invention, the scope of which is defined by the appended claims.

Example 1: Method for making a bioactive implant

400 mg PDLLA (poly(D,L) lactide, Resomer R 203 by Boehringer-Ingelheim) is dispersed in 6 ml chloroform at room temperature. If the coating is to contain other osteoinductive or biocidal substances, these are also added to the dispersion, in which case 400 mg is the total combined weight of the PDLLA and the additives. The dispersion is allowed to sit for 6 hours until a colloidal solution has formed, which is then passed through a sterile microfilter with a pore size of 0.45 μm into a sterile container.

Next, Kirschner wires (1.6 mm in diameter, 3.5 cm long) of titanium and steel as well as titanium bone nails are immersed in the filtered solution, whereupon the solvent is allowed to evaporate in a chloroform atmosphere for a period of 10 minutes. This process (coating and evaporation) is repeated once. The implants obtained preferably will be coated with a thin, varnish-like polymer layer about 10 to 20 μm thick.

Example 2: Microbiological properties of the coating

After an incubation time of either 6 or 12 weeks, microbiological examinations of titanium Kirschner wires coated with a layer of PDLLA according to example 1 revealed no noticeable growth of microorganisms. Additionally, ten implants coated with PDLLA and

5   ten uncoated implants were each contaminated with staphylococci (KD 10^5). The coated implants displayed a significantly lower adhesion rate of these microorganisms.

Example 3: Mechanical strength of the coating

Twenty titanium and steel Kirschner wires each were weighed and then coated, as in

10   Example 1, with PDLLA containing 1% methyl violet as color marker. The wires were implanted in the tibiae of rats. Following explantation, the mechanical abrasion of the coating was measured by weighing and by photometric analysis. The highest abrasion rate found was 2.9% in the case of titanium wires and 4.6% for steel wires. Raster electron micrographs showed that in none of the implants examined had the coating been abraded all

15   the way to the metal surface.

Example 4: Method for making a bioactive implant

This example will show the advantages of a colloidal solution for the mechanical strength of the coating. 800 mg each of PDLLA R 203 was added to 2 batches of 6 ml ethyl

20   acetate each. The resulting dispersions were allowed to sit at room temperature for either 6 or 24 hours respectively and were then filtered as in Example 1. The dispersions or solutions thus obtained were used to coat stents, employing the procedure per Example 1. It should be mentioned that although stents are not orthopaedic implants, they were used only because they are particularly well suited for elongation tests, and, as a result, for the analysis

25   of the mechanical strength of the varnish-like coating. The volume of the coating was determined by weighing the stents before and after the application of the coating. The coated stents were expanded with a PTCA balloon at a pressure of 8 bar (116 psi) using conventional techniques. The expanded stents were weighed again to determine the amount of the coating material that had peeled off or was lost some other way.

30   It was found that the stents which were coated with the dispersion that had stood for 6 hours prior to the filtering had lost an average of 0.8% of their coating while the other stents (which had stood for 24 hours) had a loss of 6.0% by weight. This indicates that for mechanical strength of the coating, it is preferable not to produce a complete chemical polymer solution in the solvent, but rather, a colloidal solution with a colloidal particle size

35   of 0.45 μm or less.

Example 5: Stability of the active agents contained in the coating

  To determine the stability of the growth factors (WF) incorporated in the coating, titanium Kirschner wires were coated with PDLLA as in Example 1, containing the growth factors IGF-I (5% by weight) and TGF-ßI (1% by weight). The stability (storage life) of the

5 growth factors was analyzed after 6 weeks, 6 months and 1 year. After 6 weeks, the loss in effectiveness was found to be less than 3%. After 6 months, the growth factors included in the coating were found to be still better than 95.5% effective; and after 1 year better than 93%. This proves that the active agents, incorporated in the coating as provided for by the invention, retain their biological stability and effectiveness even if the coated implant is

10 stored for an extended period of time before it is used.

Example 6: Biodegradation of the PDLLA coating

  Titanium Kirschner wires, coated with PDLLA per Example 1, were subjected to *in-vitro* elutriation tests. To simulate *in vivo* situations, the elutions were passed through a

15 physiological 0.9% NaCl solution at a temperature of 37°C (98.6°F) under laminar air-flow conditions. Within 9 weeks about 10% of the PDLLA coating had progressively degraded. For an *in vivo* study of the biodegradation characteristics of the PDLLA coating, 10 PDLLA-coated Kirschner wires with a defined coating volume were implanted in Sprague Dawley rats. After 6 weeks, the implants were removed and the *in vivo* degradation of the

20 PDLLA coating was determined by measuring the difference between the pre-implantation and the post-explantation weight, as well as the inherent viscosity, and the molecular weight of the completely separated coating, followed by a comparison with the *in vitro* data.

  As shown in Fig. 1, about 10% of the PDLLA coating had biodegraded within 9 weeks. The comparative *in vivo* measurement shows that at that point in time, the *in vitro*

25 and *in vivo* results were fairly identical.

Example 7: Examination of the release of active agents integrated in the coating

  As in Example 1, titanium Kirschner wires were coated with PDLLA, which additionally contained either 5% by weight of IGF-I or 1% by weight of TGF-ß1 or a

30 combination of 5% by weight of IGF-I and 1% by weight of TGF-ß1. The release pattern of the growth factors incorporated in the coating was analyzed with *in vitro* elutriation tests. The results are shown in Fig. 2. Within 48 hours, an initial release of growth factors from the coating took place at a rate of 48 to 54%. From there, the release continued progressively until after 6 weeks, a total of between 71 and 78% of the growth-factor

35 inclusions were released.

Ten titanium Kirschner wires, coated with PDLLA and the above-mentioned growth factors, were implanted in the tibiae of each of the Sprague Dawley rats used. After 42 days, the implants were removed and the residual concentrations of the growth factor inclusions were measured, using ELISA. As shown in Fig. 2, the *in vivo* results matched

5 those of the *in vitro* elutriation tests.

Example 8: Osteoinductive effect of the implants

In an experiment with animals, tests were conducted on 60 such animals (5-months-old female Sprague Dawley rats). All test animals were subjected to a standardized fracture

10 of the right tibia. Differently coated titanium wires (1.0 mm in diameter) were then implanted in the repositioned tibiae as intramedullary supports.

Depending on the group assignments as specified below 2 mg/kg of a rat-specific recombinant growth hormone (r-rGH) or a placebo was subcutaneously injected daily for a period of time up to 42 days. At various time points (0 d, 4 d, 7 d, 14 d, 21 d, 28 d, 35 d,

15 and 42 d) and after administration of an anaesthetic inhalant, x-rays were taken in two planes, 1.25 ml of blood was taken from each by the retrobulbar method (deep-frozen at -80°C (-112°F)), and their weight and body temperature were measured. On day 42, the fractured and the unfractured tibiae, along with the periosteum, were separately prepared and subjected to biomechanical tests (torsional load - torsional stiffness).

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Group assignments

Group I: Fracture of the right tibia - uncoated implant -
             Systemic application of a placebo (control group)

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Group II: Fracture of the right tibia - implant coated with poly-D,L-lactide 203 -
             Systemic application of a placebo

Group III: Fracture of the right tibia - implant coated with poly-D,L-lactide -
30   Systemic application of (r-rGH)

Group IV: Fracture of the right tibia - implant coated with
             poly-D,L-lactide and growth factors IGF-I (5%) and TGF-β (1%) -
             Systemic application of a placebo

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Group V: Fracture of the right tibia - implant coated with
          poly-D,L-lactide and growth factors IGF-I (5%) and TGF-β (1%) -
          Systemic application of (r-rGH)

5   The coated implants were produced as indicated in Example 1.

Results:
Fracturing

The fracturing model employed lent itself well to the creation of a standardized
10 transverse fracture of the right tibia, without any major damage to the soft tissue. In 2 out of
60, the tibia fracture was comminuted; in one, it was helical, requiring premature
discontinuation. One animal died in a postoperative examination under anesthesia (32nd
day).

15 Weight and temperature

In the animals systemically treated with (r-rGH) (Groups III and V), there was no
rise in body temperature during the course of the test, in comparison to the animals that had
been given a placebo (Groups I, II and IV), but their body weight increased significantly by
13% ($p < 0.05$). No major differences were found among Groups I, II and IV (placebo) or III
20 and V (GH).

Biomechanical test

The data obtained are expressed in absolute values (torsional load) and in
percentages (torsional stiffness), as compared to the unfractured opposite side. The results
25 reveal a significant increase ($p < 0.05$) of the maximum torsional load in Group III, as well as
Groups IV and V, as compared to the systemic application. It appears that the local
application of growth factors (Group IV) not only leads to a markedly higher maximum
torsional load, compared to the control group, but on average also when compared with the
results of the systemic application of r-rGH (insignificant). No further increase in the
30 maximum torsional load was observed as a result of simultaneous administration of r-rGH
and the local application of IGF-I and TGF-β. The maximum torsional load in the group
treated with poly-D,L-lactide increased significantly, compared to that of the control group.
In terms of torsional stiffness, relative to that of the contralateral tibia, comparable findings
were made. In this case as well, the groups with the local application of growth factors
35 showed the most favorable results. Fig. 9 summarizes these results.

Example 9:

5 months-old female Sprague Dawley rats (n=144) were subjected to a standardized closed fracture of the right tibia using a fracturing machine; and uncoated versus coated titanium Kirschner wires were implanted in the tibiae as intramedullary stabilizers. A
5 comparison was made between the following groups:

Group I: Uncoated implant (control group)

Group II: Implant coated with PDLLA ® 203)
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Group III: Implant coated with PDLLA + r-IGF-I (5%)

Group IV: Implant coated with PDLLA + r-IGF-I (5%) + TGF-β1 (1%)

15   The coated implants were produced as in Example 1. Time-sequential radiographs were taken in 2 planes (a.-p. and lateral). At time points 0 d, 4 d, 7 d, 14 d, 21 d, 28 d, sera were measured, including the systemic concentration of r-IGF-I and r-TGF-β1 and the body weight and body temperature were determined. After 4 weeks, the implants were removed and the fractured tibiae were biomechanically tested in comparison with the untreated
20 contralateral tibiae. The histomorphometric examination (O. Safranin/v.Kossa) of the calli was quantified by means of an analytical imaging system (Zeiss KS 400).

In the radiographic evaluation, the untreated Group I still showed a distinct fractured dissociation. Groups II and III displayed good callus formation, as compared to the uncoated Group I. In the animals of Group IV, the fractures had almost completely
25 consolidated (Fig. 3). Compared to the untreated contralateral tibia, and in a comparison with all other groups, the biomechanical tests revealed for Group IV a significantly higher maximum torsional load and maximum torsional stiffness. The combined application of r-IGF-I and r-TGF-β1 produced a substantially higher maximum torsional load and maximum torsional stiffness, compared to the group treated with IGF-I. The group treated with
30 polylactide showed a significantly higher maximum torsional load and maximum torsional stiffness than the untreated Group I (Fig. 4).

The histomorphometric examinations substantiate the radiographic and biomechanical test results. There were substantially more areas of connective tissue cells in Group I than in the treated groups. The group treated with PDLLA displayed good callus
35 formation and a pattern of advanced callus reconstruction, with a minimal proportion of

connective tissue cells. Group IV displayed an almost completely restored fracture and the highest bone density in the callus. The group treated with polylactide only also showed a significantly higher bone density in the callus area, as compared with the control group (Fig. 5 and 6).

5   Between the treated and the untreated groups, no changes were evident in terms of serum parameters, body weight, or body temperature.

Example 10:

        12 months-old Yucatan dwarf pigs (n=30) were subjected to a standardized

10 osteotomy (1 mm gap) of the right tibia which was then intramedullarily stabilized with either coated or uncoated titanium tibia nails and statically locked. A comparison of the following groups was made:

Group I: Uncoated implant (control group)

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Group II: Implant coated with PDLLA ® 203)

Group III: Implant coated with PDLLA + r-IGF-I (5%) + TGF-β1 (1%)

20   The coated implants were produced as in Example 1. Time-sequential radiographic examinations and serum tests were performed. After 4 weeks, the two tibiae were removed and biomechanically tested. The callus diameter was measured and the callus volume was determined by the Archimedes principle.

25 Results:

        After 4 weeks, all of the control-group animals showed an incomplete consolidation of the osteotomy gap. The group treated with polylactide showed good callus formation. Group III displayed substantially advanced callus formation (Fig. 7). In Group II, treated with polylactide, and Group III, additionally treated with growth factors, the callus volume

30 and callus diameter were significantly greater than in the control group.

        Compared to the contralateral tibia, and in comparison with the control group, the group treated with polylactide displayed a considerably higher maximum torsional load and maximum torsional stiffness. The inclusion of growth factors in the polylactide coating produced a significant augmentation of the maximum torsional load and maximum torsional

35 stiffness.

Strength of the intramedullary support

       The standardized explantation of the titanium wires from the tibiae, using a power extractor, required substantially more extractive force for explanting the wires coated with IGF-I and TGF-β than those in the control group.

5   It is evident from Examples 8 to 10 that the use of an implant coated with a varnish-like biodegradable polymer coating can significantly accelerate the osteosynthesis and thus the healing process of the fracture. This accelerated process has been documented for a polymer-coated implant, without the addition of other osteoinductive agents. Incorporating growth factors in the coating permits a further acceleration of the fracture-healing process,

10 with the combined application of IGF-I and TGF-β being particularly effective.

       The examples also show that by means of the method per this invention, it is possible to produce a varnish-like coating, which by virtue of its physical structure and mechanical strength clearly distinguishes itself from any prior art.

       While various descriptions of the present invention are described above, it should be

15 understood that the various features can be used singly or in any combination thereof. Therefore, this invention is not to be limited to only the specifically preferred embodiments depicted herein.

       Further, it should be understood that variations and modifications within the spirit and scope of the invention may occur to those skilled in the art to which the invention

20 pertains. Accordingly, all expedient modifications readily attainable by one versed in the art from the disclosure set forth herein that are within the scope and spirit of the present invention are to be included as further embodiments of the present invention. The scope of the present invention is accordingly defined as set forth in the appended claims.

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